IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Buechler *et al.*

Title: DIAGNOSTIC MARKERS OF STROKE AND CEREBRAL INJURY AND METHODS OF USE THEREOF

Appl. No.: 10/673,077

Filing Date: September 26, 2003

Examiner: Lisa V. Cook

Art Unit: 1641

DECLARATION OF DR. KENNETH F. BUECHLER

I, Kenneth F. Buechler, Ph.D., state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently President and Chief Scientific Officer for Biosite Incorporated, San Diego, CA, the assignee of U.S. Patent Application No. 10/225,082 ("the '082 application"). I am named as a joint inventor on the '082 application. A copy of my *curriculum vitae* is attached to my declaration as Appendix A. I have worked in the field of immunodiagnostics for about 20 years and am an inventor on more than 50 patents in this field.

3. I have reviewed and am familiar with the above referenced patent application, and the most recent Office Action mailed on September 2, 2006. I understand that the Examiner contends that the phrases "markers related to" and "markers related thereto" are indefinite because "the characteristics needed to determine whether an unknown could be considered to be [related to a marker are] unknown." Office Action, page 6. I also understand that the proper

standard to be applied is whether one skilled in the art would understand the bounds of the claim when read in the light of the specification.

4. For the following reasons I disagree with the Examiner's view, and conclude that the skilled artisan would clearly understand the bounds of the claims. First of all, I note that the specification at paragraph [0093] provides a clear definition with regard to the relationship between a particular named marker and those markers that are "related thereto":

> The term "related marker" as used herein refers to one or more fragments of a particular marker or its biosynthetic parent that may be detected as a surrogate for the marker itself or as independent markers. For example, human BNP is derived by proteolysis of a 108 amino acid precursor molecule, referred to hereinafter as BNP1-108. Mature BNP, or "the BNP natriuretic peptide," or "BNP-32" is a 32 amino acid molecule representing amino acids 77-108 of this precursor, which may be referred to as BNP77-108. The remaining residues 1-76 are referred to hereinafter as BNP1-76.

In my opinion, this definition alone makes the bounds of the present claims clear to one skilled in the art. To use the Examiner's characterization, the artisan will immediately appreciate that "the characteristics needed to determine whether an unknown could be considered to be related" to a particular named marker are provided by the known amino acid sequence of the marker and their known biosynthetic parent.

5. Although not necessary, the specification also presents in paragraphs [0092]-[0098] an example that further elaborates on the relationship between a particular named marker and those markers that are "related thereto." This example uses BNP and its biosynthetic parent to make the point that markers are often synthesized as "pro" forms that are cleaved, resulting in several possible polypeptides that all stem from the same parent, and that are often found in circulation together. In addition, the example states that such polypeptides are often cleaved by circulating proteases, and refers to fragments of BNP and its biosynthetic parent, again as an example to the skilled artisan.

6. The Examiner also asserts that the specification does not teach how to define or obtain "markers related to" the various markers recited in the claims (Office Action, page 7) and, as such, the skilled artisan cannot envision the detailed structure of such markers (*see, e.g.*, Office Action, page 8). I disagree with this view, which ignores both the extensive guidance to the artisan in this regard provided by the specification, as well as the very nature of the invention being claimed. As discussed in detail in, for example, paragraphs [0203]-[0210], the assays described in the claims are typically immunoassays, which are specific binding assays in which antibodies are used to detect a molecule of interest. The skilled artisan understands that, depending on the assay type, a single antibody (*e.g.*, in a competitive immunoassay) or perhaps two antibodies (*e.g.*, in a sandwich immunoassay) may be used to detect a particular marker. Because an antibody epitope is on the order of 8 amino acids (a size perhaps two orders of magnitude smaller than the average protein), *an assay can, by its very nature, detect "related" polypeptides*, so long as the polypeptides contain the epitope(s) necessary to bind to the antibody or antibodies used in the assay. The language used in the present claims simply reflects this basic fact concerning such assays.

7. This understanding of the nature of the invention being claimed is supported by large body of knowledge available to the skilled artisan. Rather than belabor this indisputable fact, I'll refer to U.S. Patent 6,235,489 as providing evidence of the understanding and acceptance by artisans of the type of claim language to which the Examiner objects. Claim 1 of the '489 patent refers to "confirming occurrence of a hemorrhagic cerebral event or an ischemic cerebral event" using a combination of four markers. One of these markers is referred to as a "brain endothelial cell membrane protein," a large class of proteins that presumably includes undisclosed and as yet undiscovered proteins. With regard to the markers, the '489 patent informs the artisan that "[t]hese proteins can be either in their native form or immunologically detectable fragments of the protein resulting, for example, by enzyme activity from proteolytic breakdown. The specific four primary markers when mentioned in the present application,

including the claims hereof, are intended to include fragments of the proteins which can be immunologically detected" (emphasis added).

8. The skilled artisan also understands that it would be a simple matter to add a proteolytic enzyme to samples to be tested, followed by detection of one or more polypeptides that are "related" to a particular marker of interest in that they are fragments generated by proteolysis. Again, such assays are typically immunoassays, and can take advantage of the fact that the proteolyticaly derived "related markers" can bind to the same antibodies as the parent marker itself. In fact, again using BNP-related polypeptides as an example, such assays have been described in the art. *See, e.g.*, Goetze *et al.*, "Quantification of pro-B-type natriuretic peptide and its products in human plasma by use of an analysis independent of precursor processing," *Clin. Chem.* 48: 1035-42, 2002 (Copy attached).

9. To summarize, the skilled artisan understands that the phrase "related marker" as recited in the claims refers to portions of a particular named marker or its biosynthetic parent, and that are bound in performing the claimed assays. This understanding is made clear throughout the specification, and is consistent with the nature of the invention being claimed and with the knowledge available in the art. Moreover, in view of the teachings of the instant patent application and the knowledge available in the art, to limit the claims to simply measuring the marker itself would be unfair, and could result in a claim that would make no sense from the perspective of the skilled artisan.

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under § 1001 of Capital Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

10/24/06
Date

Kenneth F. Buechler
Dr. Kenneth F. Buechler